ATTORNEY DOCKET NUMBER: 2002834-0043 (CIP4)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Bannon, et al.	Examiner:	Huynh, P.
Serial No.:	09/141,220	Art Unit:	1644
Filed:	August 27, 1998		
For:	METHODS AND REAGENTS FOR DECREASING CLINICAL REACTIONS TO ALLERGY		

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APPEAL BRIEF UNDER 37 C.F.R. § 1.192

Appellant appeals to the Board of Patent Appeals and Interferences (the "Board") from the Examiner's rejection of claims 37-54 and 57-62. A Notice to this effect was filed pursuant to 37 C.F.R. § 1.191(a) on December 5, 2003. The Advisory Action mailed January 6, 2004 indicates that the Notice was received by the Patent and Trademark Office on December 8, 2003.

Filed herewith is a Petition under 37 C.F.R. § 1.136 for a five (5) month extension of time, from February 8, 2004, up to and including July 8, 2004, to file this Appeal Brief (the "Brief"). Pursuant to 37 C.F.R. § 1.192(a), this Brief is being filed in triplicate.

Also enclosed are checks to cover the $1005.00 fee under 37 C.F.R. § 1.17(a)(5) for the Petition and the $165.00 fee under 37 C.F.R. § 1.17(c) for the Appeal Brief. Please charge any additional fees (or credit any overpayment), to our Deposit Account 03-1721.

Real Parties in Interest

As a result of assignments by the inventors, the real parties in interest in this application are the University of Arkansas ("UArk"), SEER Pharmaceuticals LLC (f/k/a Panacea Pharmaceuticals, LLC), and the Mt. Sinai School of Medicine of the City University of New York ("Mt Sinai"). An assignment from inventors Garry Bannon and Wesley Burks to UArk was recorded in the Patent and Trademark Office on April 23, 1999 at Reel 010065, Frame 0008. An assignment from inventor

Howard Sosin to Panacea Pharmaceuticals, LLC was recorded in the Patent and Trademark Office on August 26, 1999 at Reel 010190, Frame 0516. A Certificate of Amendment changing the name of Panacea Pharmaceuticals, LLC to SEER Pharmaceuticals, LLC was filed with the Secretary of State of the State of Delaware on October 25, 2002. A copy of this Certificate was filed for recordation with the Patent and Trademark Office on October 16, 2003. An assignment from inventor Hugh Sampson to Mt Sinai was recorded in the Patent and Trademark Office on October 22, 1998 at Reel 009539, Frame 0550.

Related Appeals and Interferences

Appellant has filed Appeal Briefs for co-pending applications U.S. Serial No. 09/455,294 (Original Brief filed October 10, 2003 and Amended Brief filed June 1, 2004); U.S. Serial No. 09/478,668 (Original Brief filed June 12, 2003 and Amended Brief filed March 23, 2004); and U.S. Serial No. 09/731,375 (Original Brief filed October 10, 2003 and Amended Brief filed June 1, 2004) addressing some issues that overlap with the issues presented here. Appellant also expects to file an Appeal Brief for co-pending application U.S. Serial Nos. 09/494,096 addressing some issues that overlap with the issues presented here. No other pending appeals or interferences are known to Appellant, Appellant's legal representative, or Appellant's assignee that will directly affect or be directly affected by the Board's decision in this appeal. Similarly, no other pending appeals or interferences are known that may have a bearing on the Board's decision in this appeal.

Status of Claims

The application was filed with claims 1-36. Claims 1-36 were the subject of a Restriction Requirement mailed June 22, 1999; claims 1-13 were elected. Claims 1-13 were examined in an Office Action mailed April 11, 2000. Claims 14-36 were canceled in an Amendment filed September 11, 2000; claim 8 was amended. Claims 1-13 were canceled in an Amendment filed August 22, 2002; claims 37-62 were added. Claims 37-62 were finally rejected in an Office Action mailed October 3, 2003. A Notice appealing the rejection of claims 37-62 was filed December 5, 2003. An Amendment canceling claims 55-56 and amending claims 57-62 was filed with the Notice. An Advisory Action was mailed January 2, 2004 indicating that the Amendment had been entered. Thus, claims 37-54 and 57-62 are pending and stand rejected. The rejection of claims 37-54 and 57-62 is hereby appealed. A listing of pending claims 37-54 and 57-62 is provided as **Attachment I**.

Status of Amendments

This Brief is being submitted together with an Amendment that amends independent claims 37 and 52 to clarify that the modified allergen is derived from a natural allergen. Claim 43 is also amended in order to clarify its scope, in particular to clarify that the portion of the allergen includes all of the one or more IgE binding sites of the natural allergen. Appellant respectfully submits that this Amendment should be entered since it adds no new matter. A copy of claims 37-54 and 57-62 that will be pending after entrance of the Amendment is provided as **Attachment II**. For the purpose of this Brief, Appellant is assuming that the Amendment will be entered. Accordingly, in the following the issues on appeal will be discussed as if they applied to the claims that will be pending *after* entrance of the Amendment.

Summary of Invention

The present invention is directed to a method of preparing modified protein allergens that have a reduced ability to bind IgE antibodies. The modified protein allergens are useful in treating allergies and in particular anaphylactic allergies. The modified protein allergens are prepared by identifying one or more IgE binding sites in a natural protein allergen; modifying the protein allergen by mutating at least one amino acid in one or more IgE binding sites; screening for IgE binding to the modified protein allergen using serum IgE from an individual that is allergic to the protein allergen; and selecting the modified protein allergens which have decreased binding to IgE as compared to the unmodified protein allergen. Claims 52-54 and 57-62 recite methods of preparing modified *food* allergens. The present specification includes data and working examples demonstrating the method as applied to peanut allergens Ara h 1, Ara h 2 and Ara h 3 (see Examples 1-2). *In vitro* (see Examples 3-4) and *in vivo* (see Example 5) experiments that were performed with a modified Ara h 2 protein are also discussed. The specification also describes other known protein allergens, including a range of food allergens, that can be modified according to the methods of the invention.

Issues

The issues on appeal are (referring to §§ **4-20** of Office Action mailed October 3, 2003):

(1) Are the pending claims invalid for lack of written description? Specifically, can the written description requirement ever be satisfied for claims relating to proteins without an explicit recitation in the specification of every sequence encompassed by the claims (§ **4**)?

(2) Are claims 57-61 invalid for containing new matter (§ **5**)?

(3) Are claims 37-39 indefinite for reciting the term "substantially" (§ **6**)? Appellant notes that the term "substantially" is not used in claim 37. Thus the rejection presumably only applies to claims 38-39.

(4) Are claims 37, 39-43, 46-47, 49-51 and 57-62 anticipated by Aki et al. (§ **9**)?

(5) Are claims 37-38, 41-43, 45-47, 49-51 and 57-62 anticipated by U.S. Pat. 5,547,669 (§ **10**)?

(6) Are claims 37, 40-43, 48-53 and 57-62 anticipated by Burks et al. (§ **12**)?

(7) Are claims 37, 40-43, 48-53 and 57-62 anticipated by Stanley et al. (§ **13**)?

(8) Are claims 37-38 and 49 obvious in light of Aki et al. and WO 94/11512 (§ **16**)?

(9) Are claims 37 and 44 obvious in light of Aki et al. and U.S. Pat. 6,207,646 (§ **17**)?

(10) Are claims 37, 48 and 52-54 obvious in light of Aki et al. in view of Burks et al., Stanley et al. or U.S. Pat. 5,449,669 (§ **18**)?

(11) Are claims 37, 39-40 and 44 obvious in light of U.S. Pat. 5,547,669 in view of Aki et al. and U.S. Pat. 6,207,646 (§ **19**)?

(12) Are claims 37, 48 and 52-54 obvious in light of U.S. Pat. 5,547,669 in view of Burks et al., Stanley et al. or U.S. Pat. 5,449,669 (§ **20**)?

Grouping of Claims

For ease of discussion, Appellant defines the following groups of claims (A)-(B):

(A) Claims 37-51 and 57-62 as dependent from claim 37 that recite a method of making a modified protein allergen.

(B) Claims 52-54 and 57-62 as dependent from claim 52 that recite a method of making a modified food allergen.

The claims stand or fall together for issues numbered (1)-(12) above, as indicated below:

(1) The claims of Group A stand or fall together and the claims of Group B stand or fall together.

(2) Claims 57-61 stand or fall together.

(3) Claim 37 stands or falls alone; claims 38-39 stand or fall together.

(4) Claims 37, 39-43, 46-47, 49-51 and 57-62 stand or fall together.

(5) Claims 37-38, 41-43, 45-47, 49-51 and 57-62 stand or fall together.

(6) Claims 37, 40-43, 48-53 and 57-62 stand or fall together.

(7) Claims 37, 40-43, 48-53 and 57-62 stand or fall together.

(8) Claims 37-38 and 49 stand or fall together.

(9) Claims 37 and 44 stand or fall together.

(10) Claims 37, 48 and 52-54 stand or fall together.

(11) Claims 37, 39-40 and 44 stand or fall together.

(12) Claims 37, 48 and 52-54 stand or fall together.

Argument

ISSUE 1: The pending claims are not invalid for lack of written description

The pending claims stand rejected for lack of written description (see § **4** of Office Action mailed October 3, 2003). With respect to this rejection, the claims of Group A stand or fall together and the claims of Group B stand or fall together.

The written description requirement imposes a duty on patent Appellants to notify the public of the scope and content of their inventions. The requirement is satisfied if one skilled in the art would reasonably conclude that the inventors were in possession of the claimed invention at the time the patent application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Furthermore, there is a strong presumption that claims submitted with an application are adequately described by the application. *In re Wertheim* 541 F.2d 257 (Fed. Cir. 1993). Claims 37-50 were present in substantially the same form as claims 1-13 in the application as originally filed. Claim 51 is a dependent claim that recites limitations found on page 4, lines 10-13 and page 9, line 17 to page 10, line 3 of the specification as filed. Claims 52-54 parallel the language of claim 37 and are of narrower scope (i.e., they are simply limited to food allergens that are described on page 8 and in the Examples). Claims 57-61 recite the limitations found in original claim 14 and the data of Table 6 of the specification as filed (see discussion under Issue 2 below). Claims 62 and 70 recite a limitation found in the section spanning pages 24-25 of the specification as filed. The burden is therefore on the Examiner to overcome the strong presumption of descriptive support with evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Examiner has not, and cannot meet this burden; the claimed invention is appropriately described in the specification.

Both in her written rejections and in an in-person interview, the Examiner has indicated that, in her view, the written description requirement can never be satisfied for a claim that involves a

nucleic acid or protein unless the complete sequence of every nucleic acid or protein to which the claim relates is explicitly set forth in the specification and recited in the claim by way of a SEQ ID NO. The same Examiner is responsible for the prosecution of a large number of related cases; we are unable to move prosecution forward without first resolving the question of whether the written description requirement can ever be satisfied without recitation of a SEQ ID NO. in the claim.

In the present case, the Examiner is taking the position that the written description cannot be satisfied for a *method of making* a modified protein allergen unless the sequence of every modified protein allergen that can be made by the method is recited. This is not the law. The legal standard for the written description requirement was most recently articulated in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). In that case, the specification described the cloning of cyclooxygenase-2 (or "COX-2") and methods of identifying selective inhibitors of COX-2. The *only* description of the inhibitors themselves consisted of the following two sentences (see column 27, lines 29-35 of U.S. Pat. No. 6,048,850):

> "The compounds identified in the screen will demonstrate the ability to selectively modulate the expression of [COX-2]. These compounds include but are not limited to nucleic acid encoding [COX-2] and homologues, analogues, and deletions thereof, as well as antisense, ribozyme, triple helix, antibody, and polypeptide molecules and small inorganic molecules."

The Patent Office issued claims to methods of selectively inhibiting COX-2 in a host by administration of such inhibitors (see claims 1-8 of U.S. Pat. No. 6,048,850). In *Rochester*, the court held that U.S. Pat. No. 6,048,850 did not include a written description of the selective inhibitors. *Id.* at 926-27. The court further held that methods of *using* the inhibitors could not be described without a written description of inhibitors and thus that the issued claims were invalid. *Id.* at 927. However, the court also held that methods of *identifying* the same inhibitors *were* adequately described and were therefore valid (these were claimed in U.S. Pat. No. 5,837,479). *Id.* at 928. Here, the pending method of *making* claims are most analogous to methods of *identifying*, not methods of *using*. Moreover, in the present case, the specification *does* contain extensive description of modified protein allergens that can be prepared according to the claimed methods. If the description was sufficient in *Rochester* then it must be adequate in the present case.

The absurdity of the Examiner's position is demonstrated by considering her rejection of the method of making modified peanut allergens that are explicitly exemplified in the specification.

According to the Examiner, the written description is not satisfied in this case for *any* nucleotide molecules other than those encoding peanut allergens that have been modified by substitution with *alanine* or *methionine* at those *specific locations* listed in Tables 4, 5 and 6. This is clearly not the law nor should it be. The proper legal question is not "did Appellant *reduce to practice* and *explicitly recite* a method of making every modified peanut allergen that falls within the scope of the claims?" Instead, the question is "would a skilled person recognize that Appellant was in *possession* of the method of making modified peanut allergens that fall within the scope of the claims?"

The present specification sets forth the complete amino acid sequences of Ara h 1, 2, and 3 (SEQ ID NOs. 2, 4 and 6), and also the nucleotide sequences of genes that encode them (SEQ ID NOs. 1, 3 and 5). The specification further sets out the amino acid sequences of each of 23 IgE epitopes mapped in the Ara h 1 protein (Table 1), the amino acid sequence of each of 10 IgE epitopes mapped in the Ara h 2 protein (Table 2), and the amino acid sequence of each of 4 epitopes mapped in the Ara h 3 protein (Table 3). The specification further describes particular alanine or methionine substitutions that were introduced into the mapped IgE binding sites, and shows that some of these substitutions result in decreased IgE binding (Tables 4-6). In discussing these data, the specification states (see page 25, lines 11-23):

> "The results discussed above for Ara h 1, Ara h 2, and Ara h 3 demonstrate that once an IgE binding site has been identified, it is possible to reduce IgE binding to this site by altering a single amino acid of the epitope. [...] Besides finding that many epitopes contained more than one residue critical for IgE binding, it was also determined that more than one residue type (ala or met) could be substituted at certain positions in an epitope with similar results. This allows for the design of a hypoallergenic protein that would be effective at blunting allergic reactions for a population of peanut sensitive individuals."

Thus, the specification specifically highlights that substitutions at different positions, and with different amino acids, achieved comparable results.

The Examiner is correct that the specification does not explicitly set forth the sequences of *all* possible disruptions to Ara h 1, Ara h 2, and Ara h 3 IgE sites. However, a skilled person, reading the specification, would understand, indeed would explicitly be told, that the presented substitutions were merely exemplary and others would work as well. A skilled artisan would appreciate that the techniques described in the specification would successfully identify all such substitutions. That is, a skilled person would understand that the inventors were in *possession* of the invention to the full scope of the claims.

A claim limited to the particular substitutions that the inventors happened to have made prior to filing their patent application is virtually useless. Anybody of ordinary skill in the art could make a modified peanut allergen that falls outside the scope of such a claim but still embodies the spirit, scope, and teachings of Appellant's contribution. If the legal standard of written description in fact required verbatim recitation of every possible useful sequence, as asserted by the Examiner, patent applicants would be forced to perform useless and wasteful experiments (potentially endlessly) merely to ensure that they could protect their contributions, or alternatively would be motivated to include endless lists of sequences in their patent applications merely to ensure that all contemplated embodiments are "described". Such a result would have no beneficial purpose.

Turning to the specifically rejected claims, claim 52, the only independent claim in Group B, recites:

> "A method of making a modified food allergen which is less reactive with IgE comprising:
> (a) identifying one or more IgE binding sites in a food allergen, the one or more IgE binding sites being ones that are recognized when the food allergen is contacted with serum IgE from an individual that is allergic to the food allergen;
> (b) modifying the food allergen by mutating at least one amino acid in one or more IgE binding sites;
> (c) screening for IgE binding to the modified food allergen using serum IgE from an individual that is allergic to the food allergen; and
> (d) selecting the modified food allergens which have decreased binding to IgE as compared to the unmodified food allergen."

The specification explicitly sets out the sequence of several examples of methods of preparing modified peanut allergens. These modified peanut allergens are described as "exemplary" of the inventive principles. For example, the specification recites that "Peanut allergens (Ara h 1, Ara h 2, and Ara h 3) have been used in the examples to demonstrate alteration of IgE binding sites while retaining binding to IgG and activation of T cells" (page 4, lines 15-17). The specification also points to several other common food allergens (see page 8, lines 1-3: "Examples of common food allergens include proteins from peanuts, milk, grains such as wheat and barley, soybeans, eggs, fish, crustaceans, and mollusks."). Moreover, the specification provides references for food allergens *whose IgE epitopes had already been* identified (see page 8, lines 4-13). The specification also describes techniques for modifying sequences within IgE sites (see, for example, page 10, lines 3-6 and Examples 2-3), and for identifying those modifications that reduce IgE binding (see, for example,

page 4, lines 24-28 and Examples 1-2) in accordance with claim 52.

And, of course, the specification provides evidence that the inventive strategy successfully produced modified peanut allergens with reduced IgE reactivity. The teachings and guidance provided by this success are far-reaching. As discussed above and in the specification, peanut allergy is one of the most potent allergies. Indeed, as noted in the specification (see page 16, lines 4-11):

> "Peanut allergy is one of the most common and serious of the immediate hypersensitivity reactions to foods in terms of persistence and severity of reaction. [...] The majority of cases of fatal food-induced anaphylaxis involve ingestion of peanuts [...]."

A person of ordinary skill in the art would immediately understand the exciting implications of the inventive exemplification of reduced-allergenicity peanut allergens: if it works for peanuts, it will work for other food allergens.

Modified food allergens produced according to the claimed methods are all proteins; sensitized individuals are exposed to them all by the same route (i.e., ingestion); they are all readily modified according to the same techniques, and those with reduced allergenicity are identified in the same manner. Reading the present specification, those of ordinary skill in the art will immediately appreciate that modified food allergens with reduced allergenicity, according to the present claims, exist, and can readily be made according to the teachings of the specification. In other words, those of ordinary skill in the art will immediately appreciate that the inventors were *in possession of* the claimed invention. Denial of claims to methods of making modified food allergens would deprive the present inventors of protection commensurate in scope with their contribution, and would create silly incentives disruptive to science, the patent process, and commerce. For all of these reasons, the Examiner's rejection of claims in Group B for lack of written description, should be removed.

The rejection for lack of written description should also be removed for the claims of Group A, which stand or fall together for the purposes of this rejection. These claims are broader than those of Group B in that they do not limit the category of protein allergen whose IgE epitopes are modified. Although the claims are broad, there is no failure of written description.

The specification makes clear that the inventive principles are applicable to *any* allergen (see, for example, page 4, lines 2-14; page 7, line 26 to page 9, line 15; and page 29, lines 18-20). The specification also specifically lists a variety of relevant allergens (see, for example, page 8, lines 13-16: "Other allergens include proteins from insects such as flea, tick, mite, fire ant, cockroach, and bee

as well as molds, dust, grasses, trees, weeds, and proteins from mammals including horses, dogs, cats, etc."). The specification includes extensive discussion of latex allergens, in particular, and provides references reporting IgE epitopes within these allergens (see, for example, page 8, line 19-page 9, line 15). The specification further recites methods of screening for the properties of claims 38-39 and 45 (e.g., see page 4, lines 8-14 and 26-28) and methods for performing the specific modifications of claims 40-43 (e.g., see page 4, lines 17-23 and the Examples). The specification also specifically points to the use of adjuvants having the characteristics recited in claim 44 (e.g., see page 15, lines 19-20) and to the preparation of recombinantly modified allergens as recited in claims 46-47 (e.g., see page 12 and Example 3). Likewise, the specification specifically recites relevant subsets of antigens recited in claims 48-49 (e.g., pages 7-9 and the Examples).

All of this information explicitly set forth in the specification, combined with the potent demonstration of success with the most challenging allergens, clearly put the public on notice that the inventors were in possession of the invention to the full scope of the present claims.

Appellant appreciates that certain court decisions, including *University of California v. Eli Lilly and Co.* have been interpreted to stand for the proposition that, in certain cases, nucleic acid or protein molecules cannot be properly described in a patent specification without explicit recitation of sequence information. However, this is not such a case. First, significant sequence information *is* provided for this case. Second, as noted in the introduction to this heading, the pending claims relate to a method, not to the nucleic acids or proteins themselves. Furthermore, a determination of whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by those skilled in the art *at the time that the invention was filed. In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). In *University of California v. Eli Lilly and Co.*, the patent applications in issue were filed in 1977 and 1979; the present application was filed 20 years later. A lot happened in the intervening 20 years. Automated sequencing and synthesis technologies were developed; PCR was invented; a variety of techniques for disrupting or otherwise mutagenizing a nucleic acid sequence were standardized. Mechanical application of a "Sequence Listing or bust" rule vitiates the very purpose of the *Lily* ruling, which was to ensure that the scope of patent claims was commensurate in scope with the contribution. The present specification describes the invention of a method for making modified protein allergens for a wide variety of allergens; the pending claims are of appropriate scope.

ISSUE 2: Claims 57-61 are not invalid for containing new matter

The Examiner has questioned the support for the recitation in claims 57-61 of a step of "modifying at least 1-6, 1-5, 1-4, 1-3 or 1-2 amino acids in at least one IgE epitope of the allergen" (see § **5** of Office Action mailed October 3, 2003). With respect to this rejection claims 57-61 stand or fall together.

Appellant respectfully submits that these claims are fully supported by the specification and claims as originally filed. In particular, original claim 1 recites a step of "modifying the allergen by mutating *at least one* amino acid in an IgE binding site [...]". Original claim 1 therefore makes it perfectly clear that the present invention encompasses methods that include a step of modifying *more than one* amino acid residue within an IgE epitope. The specification as filed further teaches IgE epitopes that include 1, 2, 3, 4, 5 or 6 amino acid residues that, when altered, lead to a reduction in IgE binding (e.g., see epitopes 5, 7, 8, 9, 18 in Table 4 and epitope 4 in Table 6, respectively). The specification and claims as originally filed therefore clearly support the language of pending claims 57-61.

ISSUE 3: Claims 37-39 are not indefinite for reciting the term "substantially"

The Examiner has taken the position that claims 37-39 are indefinite under 35 U.S.C. § 112, second paragraph for reciting the term "substantially" without providing a definition of the term in the specification (see § **6** of Office Action mailed October 3, 2003). Appellant notes that the term "substantially" is not used in claim 37. Thus the rejection presumably only applies to claims 38-39. With respect to this rejection claim 37 stands or falls alone and claims 38-39 stand or fall together.

Appellant respectfully disagrees with this rejection. The courts have clearly stated that expressions such as "substantially" may be used in patent claims when warranted by the nature of invention, in order to accommodate the minor variations that may be appropriate to secure the invention. *Verve LLC v. Crane Cams*, 311 F.3d 1116 (Fed. Cir. 2002). The nature of the presently claimed invention is such that the selection of modified allergens that exhibit minor variations in T-cell activation (claim 38) or IgG binding (claim 39) as compared to an unmodified allergen could be made without losing the benefit of the present invention. One skilled in the art, upon reading the present specification, would readily recognize such trivial variations. No more is required. In fact, as noted in Judge Hand's opinion in *Musher Foundation v. Alba Trading Co.*, 326 U.S. 770 (1945):

> 'Substantially' is not of itself fatal to a claim [...] indeed, it must always be implied in every claim, even when not introduced, and adds nothing when it is. Were this not true, few patents could be given any protection, for some departures from the precise disclosure are nearly always possible without losing the benefit of the invention.

For all of these reasons, withdrawal of the rejection is earnestly requested.

ISSUE 4: Claims 37, 39-43, 46-47, 49-51 and 57-62 are not anticipated by Aki et al.

The Examiner has rejected claims 37, 39-43, 46-47, 49-51 and 57-62 under 35 U.S.C. § 102(b) as being anticipated by Aki et al. (*Int. Arch. Allergy Immunol.* 103:357-364, 1994) (see § 9 of Office Action mailed October 3, 2003). This rejection is respectfully traversed; with respect to this rejection claims 37, 39-43, 46-47, 49-51 and 57-62 stand or fall together.

In order to anticipate a claim, a reference must teach every element of the claim. MPEP § 2131. Appellant submits that Aki et al. cannot anticipate the claimed invention because it does not teach all of the steps in the presently claimed method. In particular, Aki et al. does not teach at least steps (b)-(d) of claim 37.

The Examiner suggests that Aki et al. teaches a method that includes a step of modifying an allergen by "mutating at least one amino acid in the center of IgE binding sites" (see page 4 of Office Action mailed October 3, 2003). In this context, the Examiner points to pages 360-361 of Aki et al. Appellant disagrees and respectfully submits that Aki et al. never teaches the modification of a *natural allergen* as claimed herein. Instead, Aki et al. teaches the preparation and modification of a wholly artificial β-galactosidase-Mag1-E2 fusion protein (e.g., see p. 359, column 2, last sentence and pp. 360-361). Mag1-E2 is an isolated IgE epitope that corresponds to amino acids 104-115 of the dust mite allergen *Mag 1*. β-galactosidase is a large enzyme (1024 amino acids and 116 kDa) that catalyzes the hydrolysis of terminal, non-reducing β-d-galactose residues in beta-galactosides. Thus, this artificial fusion protein is not a *natural allergen* that falls within the scope of claim 37. Certainly its sequence and physical properties bear no resemblance whatsoever to those of the natural 39 kDa dust mite allergen *Mag 1* taught by Aki et al. Nor is the fusion protein a "portion of a natural allergen that includes all of the IgE binding sites of the natural allergen" as defined in claim 43.

Since Aki et al. does not teach each and every step of the claimed methods, it cannot anticipate or render obvious claims 37, 39-43, 46-47, 49-51 and 57-62. Withdrawal of the rejection is earnestly requested.

ISSUE 5: Claims 37-38, 41-43, 45-47, 49-51 and 57-62 are not anticipated by U.S. Pat. 5,547,669

The Examiner has rejected claims 37-38, 41-43, 45-47, 49-51 and 57-62 under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat. 5,547,669 (see § **10** of Office Action mailed October 3, 2003). This rejection is respectfully traversed; with respect to this rejection claims 37-38, 41-43, 45-47, 49-51 and 57-62 stand or fall together.

As noted *supra*, in order to anticipate a claim, a reference must teach every element of the claim. MPEP § 2131. Appellant submits that U.S. Pat. 5,547,669 cannot anticipate the claimed invention because it does not teach all of the steps in the presently claimed method. In particular, U.S. Pat. 5,547,669 does not teach a method that includes steps of identifying and then mutating at least one amino acid in one or more IgE binding sites of an allergen, i.e., steps (a)-(b) of claim 37.

As noted by the Examiner, U.S. Pat. 5,547,669 teaches methods of preparing so-called "recombitope peptides" that are designed to stimulate T-cell activity (e.g., see Abstract). These peptides are essentially prepared by identifying T-cell epitopes within one or more natural protein antigens and then extracting, rearranging and pasting these together to produce wholly artificial peptides (e.g., see column 6, lines 59 to column 7, line 62).

The Examiner seems to take the position that U.S. Pat. 5,547,669 also teaches a step of identifying and mutating IgE binding sites. In this context, the Examiner points to column 15, lines 1-5 and 15-17. Appellant does not see how this section of U.S. Pat. 5,547,669 teaches the modification of IgE binding sites. Indeed, while column 15 discusses "modified recombitopes" that include an amino acid substitution, deletion or addition, there is no teaching or suggestion that these mutations should be located within IgE epitopes. In fact, U.S. Pat. 5,547,669 explicitly teaches that the mutations should be located within T-cell epitopes of the recombitopes (see column 15, lines 6-14 that was omitted from the Examiner's citation) or should disrupt disulfide bridges in order to minimize dimerization (see column 15, lines 15-19). Further, U.S. Pat. 5,547,669 specifically teaches that in order to reduce the likelihood of IgE binding, IgE epitopes are preferably *excluded* from the amino acid sequences of recombitopes altogether:

> "Those peptide regions found to bind immunoglobulin E and cause the release of mediators from mast cell or basophils in greater than approximately 10-15% of the allergic sera tested are *preferably not included* in the peptide regions arranged to form recombitope peptides". (e.g., see column 8, lines 5-9, emphasis added)

If recombitope peptides lack IgE epitopes it is presumably undisputed that their preparation cannot involve a step of "mutating at least one amino acid in one or more IgE binding sites of an allergen".

The Examiner also makes reference to column 15, lines 59-62 that describes the introduction of canonical protease sites (e.g., KK or RR) within a recombitope peptide. Again, Appellant notes that there is no teaching of locating such sites within IgE epitopes. We are only taught that they should be located between regions that comprise "at least one T-cell epitope" (see column 15, lines 59-62). We are further taught that these sites can "potentially aid proper antigen processing of T-cell epitopes within a recombitope peptide" and/or "result in an increase in solubility of the recombitope peptide" (see column 15, lines 55-56 and 65-67). IgE binding and IgE epitopes are never discussed in this context.

Since U.S. Pat. 5,547,669 does not teach each and every step of the claimed methods, it cannot anticipate or render obvious claims 37-38, 41-43, 45-47, 49-51 and 57-62. Withdrawal of the rejection is earnestly requested.

ISSUE 6: Claims 37, 40-43, 48-53 and 57-62 are not anticipated by Burks et al.

The Examiner has rejected claims 37, 40-43, 48-53 and 55-62 under 35 U.S.C. § 102(a) as being anticipated by Burks et al. (*Eur. J. Biochem.* 245:334-339, 1997) (see § **12** of Office Action mailed October 3, 2003). Claims 55-56 and 57-62 (as dependent from claim 55) have been cancelled. With respect to this rejection claims 37, 40-43, 48-53 and 57-62 stand or fall together.

This rejection should be removed quite simply because Burks et al. is not prior art. The relevant teachings of Burks et al. were included near *verbatim* in U.S. Serial No. 08/717,933 filed September 23, 1996 (see pp. 133-155 and the Figures referred to therein). The 1996 filing was made by Appellant in part to protect the teachings of Burks et al. The present application properly claims priority to this 1996 filing. Burks et al. was published after this priority date and cannot therefore be used as prior art under 35 U.S.C. § 102(a). Withdrawal of the rejection is earnestly requested.

ISSUE 7: Claims 37, 40-43, 48-53 and 57-62 are not anticipated by Stanley et al.

The Examiner has rejected claims 37, 40-43, 48-53 and 55-62 under 35 U.S.C. § 102(a) as being anticipated by Stanley et al. (*Archives of Biochemistry and Biophysics* 342(2):244-253, 1997) (see § **13** of Office Action mailed October 3, 2003). Claims 55-56 and 57-62 (as dependent from

claim 55) have been cancelled. With respect to this rejection claims 37, 40-43, 48-53 and 57-62 stand or fall together.

This rejection should also be removed quite simply because Stanley et al. is not prior art. The relevant teachings of Stanley et al. were included near *verbatim* in U.S. Serial No. 08/717,933 filed September 23, 1996 (see pp. 156-174 and 176-180). The 1996 filing was made by Appellant in part to protect the teachings of Stanley et al. The present application properly claims priority to this 1996 filing. Stanley et al. was published after this priority date and cannot therefore be used as prior art under 35 U.S.C. § 102(a). Withdrawal of the rejection is earnestly requested.

ISSUE 8: Claims 37-38 and 49 are not obvious in light of Aki et al. and WO 94/11512

The Examiner has rejected claims 37-38 and 49 under 35 U.S.C. § 103(a) as being unpatentable over Aki et al. in view of WO 94/11512 (see § **16** of Office Action mailed October 3, 2003). With respect to this rejection claims 37-38 and 49 stand or fall together.

The teachings of Aki et al. and its deficiencies with regards to claim 37 have been discussed *supra*. WO 94/11512 is a secondary reference that is cited solely as teaching limitations that are found in dependent claims 38 and 49, namely a step of screening for activation of T-cells and the use of an allergen from trees. The Examiner points to no teaching or suggestion in WO 94/11512 that could overcome the aforementioned deficiencies of Aki et al. Withdrawal of the rejection is earnestly requested.

ISSUE 9: Claims 37 and 44 are not obvious in light of Aki et al. and U.S. Pat. 6,207,646

The Examiner has rejected claims 37 and 44 under 35 U.S.C. § 103(a) as being unpatentable over Aki et al. in view of U.S. Pat. 6,207,646 (see § **17** of Office Action mailed October 3, 2003). With respect to this rejection claims 37 and 44 stand or fall together.

The teachings of Aki et al. and its deficiencies with regards to claim 37 have been discussed *supra*. U.S. Pat. 6,207,646 is a secondary reference that is cited solely as teaching limitations that are found in dependent claim 44, namely a step of formulating the modified allergen with a specific adjuvant. The Examiner points to no teaching or suggestion in U.S. Pat. 6,207,646 that could overcome the aforementioned deficiencies of Aki et al. Withdrawal of the rejection is earnestly requested.

ISSUE 10: Claims 37, 48 and 52-54 are not obvious in light of Aki et al. in view of Burks et al., Stanley et al. or U.S. Pat. 5,449,669

The Examiner has rejected claims 37, 48, 52-56 under 35 U.S.C. § 103(a) as being unpatentable over Aki et al. in view of Burks et al., Stanley et al. or U.S. Pat. 5,449,669 (see § **18** of Office Action mailed October 23, 2003). Claims 55-56 have been cancelled. With respect to this rejection claims 37, 48 and 52-54 stand or fall together.

The teachings of Aki et al. and its lackings have been discussed *supra*. As discussed *supra*, Burks et al. and Stanley et al. are not available as prior art under 35 U.S.C. § 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of Aki et al. Withdrawal of the rejection is earnestly requested.

ISSUE 11: Claims 37, 39-40 and 44 are not obvious in light of U.S. Pat. 5,547,669 in view of Aki et al. and U.S. Pat. 6,207,646

The Examiner has rejected claims 37, 39-40 and 44 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. 5,547,669 in view of Aki et al. and U.S. Pat. 6,207,646 (see § **19** of Office Action mailed October 23, 2003). With respect to this rejection claims 37, 39-40 and 44 stand or fall together.

The teachings of U.S. Pat. 5,547,669 and its lackings have been discussed *supra*. Aki et al. is cited as limitations that are found in dependent claims 39 and 40, namely a step of screening for IgG binding and mutating the allergen in the center of an IgE binding site. Additional teachings of Aki et al. are discussed *supra*. U.S. Pat. 6,207,646 is cited solely as teaching limitations that are found in dependent claim 44, namely a step of formulating the modified allergen with a specific adjuvant. The Examiner points to no teaching or suggestion in Aki et al. or U.S. Pat. 5,449,669 that could overcome the deficiencies of U.S. Pat. 5,547,669. Withdrawal of the rejection is earnestly requested.

ISSUE 12: Claims 37, 48 and 52-54 are not obvious in light of U.S. Pat. 5,547,669 in view of Burks et al., Stanley et al. or U.S. Pat. 5,449,669

The Examiner has rejected claims 37, 48, 52-56 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. 5,547,669 in view of Aki et al. and U.S. Pat. 6,207,646 (see § **19** of Office Action mailed October 23, 2003). Claims 55-56 have been cancelled. With respect to this

rejection claims 37, 48 and 52-54 stand or fall together.

The teachings of U.S. Pat. 5,547,669 and its lackings have been discussed *supra*. As discussed *supra*, Burks et al. and Stanley et al. are not available as prior art under 35 U.S.C. § 103(a). U.S. Pat. No. 5,449,669 is cited solely as teaching an unmodified protein allergen, namely shrimp tropomyosin, and its two IgE binding epitopes. The Examiner points to no teaching or suggestion in U.S. Pat. 5,449,669 that could overcome the deficiencies of U.S. Pat. 5,547,669. Withdrawal of the rejection is earnestly requested.

Conclusion

Appellant again concludes with the belief that claims 37-54 and 57-62 as amended by the Amendment filed herewith are fully supported by the specification as filed and allowable over the art of record. Allowance of these claims is earnestly requested.

Respectfully submitted,

Dated: July 8, 2004

Charles E. Lyon, D.Phil.
Limited Recognition Under 37 CFR § 10.9(b)

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Attachment I

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending before Entrance of Amendment

Claims Pending before Entrance of Amendment

1-36. **(Canceled)**

37. **(Previously presented)** A method of making a modified allergen which is less reactive with IgE comprising:

(a) identifying one or more IgE binding sites in an allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen;

(b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites;

(c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and

(d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen.

38. **(Previously presented)** The method of claim 37 further comprising screening for activation of T cells that have been cultured from an individual that is allergic to the allergen and selecting the modified allergens which activate the T cells in substantially the same way as the unmodified allergen.

39. **(Previously presented)** The method of claim 37 further comprising screening for binding of the modified allergen to IgG using serum IgG from an individual that is allergic to the allergen and selecting the modified allergens which bind IgG in substantially the same way as the unmodified allergen.

40. **(Previously presented)** The method of claim 37 wherein the modified allergen is mutated in the center of one or more of the IgE binding sites.

41. **(Previously presented)** The method of claim 37 wherein the modified allergen is mutated by substitution.

42. **(Previously presented)** The method of claim 41 wherein the modified allergen is mutated by substituting a hydrophobic amino acid in the center of one or more of the IgE binding sites with a neutral or hydrophilic amino acid.

43. **(Previously presented)** The method of claim 37 wherein the modified allergen is a portion of the allergen.

44. **(Previously presented)** The method of claim 37 wherein the modified allergen is formulated with an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and immune stimulatory oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response.

45. **(Previously presented)** The method of claim 37 wherein the modified allergen is screened for initiation of a T cell helper 1 response.

46. **(Previously presented)** The method of claim 37 wherein the modified allergen is made in a recombinant host selected from the group consisting of plants, animals, bacteria, yeast, fungi, and insect cells.

47. **(Previously presented)** The method of claim 37 wherein the modified allergen is made in cells using site specific mutation.

48. **(Previously presented)** The method of claim 37 wherein the modified allergen is made from a peanut allergen selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

49. **(Previously presented)** The method of claim 37 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes.

50. **(Previously presented)** The method of claim 37, wherein the step of modifying includes mutating at least one amino acid in all the IgE epitopes of the allergen.

51. **(Previously presented)** The method of claim 37, wherein the at least one IgE epitope is one that is recognized when the allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the allergen.

52. **(Previously presented)** A method of making a modified food allergen which is less reactive with IgE comprising:

(a) identifying one or more IgE binding sites in a food allergen, the one or more IgE binding sites being ones that are recognized when the food allergen is contacted with serum IgE from an individual that is allergic to the food allergen;

(b) modifying the food allergen by mutating at least one amino acid in one or more IgE binding sites;

(c) screening for IgE binding to the modified food allergen using serum IgE from an individual that is allergic to the food allergen; and

(d) selecting the modified food allergens which have decreased binding to IgE as compared to the unmodified food allergen.

53. **(Previously presented)** The method of claim 52 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.

54. **(Previously presented)** The method of claim 53 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.

55-56. **(Canceled)**

57. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-6 amino acids in at least one IgE epitope of the allergen.

58. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-5 amino acids in at least one IgE epitope of the allergen.

59. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-4 amino acids in at least one IgE epitope of the allergen.

60. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-3 amino acids in at least one IgE epitope of the allergen.

61. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-2 amino acids in at least one IgE epitope of the allergen.

62. **(Previously presented)** The method of claim 37 or 52 wherein the step of selecting includes selecting the modified allergens which bind to IgE at levels that are less than about 1% of those observed with the unmodified allergen.

Attachment II

to

Appeal Brief under 37 C.F.R. § 1.192

Claims Pending after Entrance of Amendment

Claims Pending after Entrance of Amendment

1-36. **(Canceled)**

37. **(Currently amended)** A method of making a modified allergen which is less reactive with IgE comprising:

(a) identifying one or more IgE binding sites in a natural allergen, the one or more IgE binding sites being ones that are recognized when the allergen is contacted with serum IgE from an individual that is allergic to the allergen;

(b) modifying the allergen by mutating at least one amino acid in one or more IgE binding sites;

(c) screening for IgE binding to the modified allergen using serum IgE from an individual that is allergic to the allergen; and

(d) selecting the modified allergens which have decreased binding to IgE as compared to the unmodified allergen.

38. **(Previously presented)** The method of claim 37 further comprising screening for activation of T cells that have been cultured from an individual that is allergic to the allergen and selecting the modified allergens which activate the T cells in substantially the same way as the unmodified allergen.

39. **(Previously presented)** The method of claim 37 further comprising screening for binding of the modified allergen to IgG using serum IgG from an individual that is allergic to the allergen and selecting the modified allergens which bind IgG in substantially the same way as the unmodified allergen.

40. **(Previously presented)** The method of claim 37 wherein the modified allergen is mutated in the center of one or more of the IgE binding sites.

41. **(Previously presented)** The method of claim 37 wherein the modified allergen is mutated by substitution.

42. **(Previously presented)** The method of claim 41 wherein the modified allergen is mutated by substituting a hydrophobic amino acid in the center of one or more of the IgE binding sites with a neutral or hydrophilic amino acid.

43. **(Currently amended)** The method of claim 37 wherein the modified allergen is a portion of the allergen, which portion includes all of the one or more IgE binding sites of the allergen.

44. **(Previously presented)** The method of claim 37 wherein the modified allergen is formulated with an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and immune stimulatory oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response.

45. **(Previously presented)** The method of claim 37 wherein the modified allergen is screened for initiation of a T cell helper 1 response.

46. **(Previously presented)** The method of claim 37 wherein the modified allergen is made in a recombinant host selected from the group consisting of plants, animals, bacteria, yeast, fungi, and insect cells.

47. **(Previously presented)** The method of claim 37 wherein the modified allergen is made in cells using site specific mutation.

48. **(Previously presented)** The method of claim 37 wherein the modified allergen is made from a peanut allergen selected from the group consisting of Ara h 1, Ara h 2, and Ara h 3.

49. **(Previously presented)** The method of claim 37 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, birds, and natural latexes.

50. **(Previously presented)** The method of claim 37, wherein the step of modifying includes mutating at least one amino acid in all the IgE epitopes of the allergen.

51. **(Previously presented)** The method of claim 37, wherein the at least one IgE epitope is one that is recognized when the allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the allergen.

52. **(Currently amended)** A method of making a modified food allergen which is less reactive with IgE comprising:

(a) identifying one or more IgE binding sites in a natural food allergen, the one or more IgE binding sites being ones that are recognized when the food allergen is contacted with serum IgE from an individual that is allergic to the food allergen;

(b) modifying the food allergen by mutating at least one amino acid in one or more IgE binding sites;

(c) screening for IgE binding to the modified food allergen using serum IgE from an individual that is allergic to the food allergen; and

(d) selecting the modified food allergens which have decreased binding to IgE as compared to the unmodified food allergen.

53. **(Previously presented)** The method of claim 52 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, and mollusks.

54. **(Previously presented)** The method of claim 53 wherein the modified allergen is based on a protein obtained from a source selected from the group consisting of wheat, barley, cow milk, egg, codfish, hazel nut, soybean, and shrimp.

55-56. **(Canceled)**

57. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-6 amino acids in at least one IgE epitope of the allergen.

58. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-5 amino acids in at least one IgE epitope of the allergen.

59. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-4 amino acids in at least one IgE epitope of the allergen.

60. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-3 amino acids in at least one IgE epitope of the allergen.

61. **(Previously presented)** The method of claim 37 or 52 wherein the step of modifying includes modifying at least 1-2 amino acids in at least one IgE epitope of the allergen.

62. **(Previously presented)** The method of claim 37 or 52 wherein the step of selecting includes selecting the modified allergens which bind to IgE at levels that are less than about 1% of those observed with the unmodified allergen.

Attachment III

to

Appeal Brief under 37 C.F.R. § 1.192

"Official list of allergens" maintained by the IUIS Allergen Nomenclature Subcommittee

printed on June 8, 2003 from ftp://biobase.dk/pub/who-iuis/allergen.list

Official list of allergens
IUIS Allergen Nomenclature Subcommittee
ftp://biobase.dk/pub/who-iuis/allergen.list

2000.03.01 Jorgen Nedergaard Larsen and Henning Lowenstein,
ALK-Abello, Boge Alle 6-8, DK-2970 Horsholm, Denmark
Please report changes, additions or comments to jnlarsen@inet.uni2.dk

Legends: MW determined by reducing SDS-PAGE; asterisk: MW deduced from sequence;
C: cDNA seq; P: peptide seq;

Allergen source	Systematic and original names	MW kDa	sequence data	Accession # or References
A. Weed pollens				
Asterales				
Ambrosia artemisiifolia				
(short ragweed)	Amb a 1; antigen E	38	C	8,20
	Amb a 2; antigen K	38	C	8,21
	Amb a 3; Ra3	11	C	22
	Amb a 5; Ra5	5	C	11,23
	Amb a 6; Ra6	10	C	24,25
	Amb a 7; Ra7	12	P	26
	Amb a ?	11	C	27
Ambrosia trifida				
(giant ragweed)	Amb t 5; Ra5G	4.4	C	9,10,28
Artemisia vulgaris				
(mugwort)	Art v 1;	27-29	C	28A
	Art v 2;	35	P	29
Helianthus annuus				
(sunflower)	Hel a 1;	34	-	29a
	Hel a 2; profilin	15.7	C	Y15210
Mercurialis annua				
	Mer a 1; profilin	14-15	C	Y13271
B. Grass pollens				
Poales				
Cynodon dactylon				
(Bermuda grass)	Cyn d 1;	32	C	30,S83343
	Cyn d 7;		C	31,X91256
	Cyn d 12; profilin	14	C	31a,Y08390
Dactylis glomerata				
(orchard grass)	Dac g 1; AgDg1	32	P	32
	Dac g 2;	11	C	33,S45354
	Dac g 3;		C	33a,U25343
	Dac g 5;	31	P	34
Holcus lanatus				
(velvet grass)	Hol l 1;		C	Z27084,Z68893

Lolium perenne				
(rye grass)	Lol p 1; group I	27	C	35,36
	Lol p 2; group II	11	C	37,37a,X73363
	Lol p 3; group III	11	C	38
	Lol p 5; Lol p IX, Lol p Ib	31/35	C	34,39
	Lol p 11; trypsin inh. Related	16		39a
Phalaris aquatica				
(canary grass)	Pha a 1;		C	40,S80654
Phleum pratense				
(timothy)	Phl p 1;	27	C	X78813
	Phl p 2;		C	41,X75925
	Phl p 4;		P	41A
	Phl p 5; Ag25	32	C	42
	Phl p 6;		C	43,Z27082
	Phl p 12; profilin		C	44,X77583
	Phl p 13; polygalacturonase	55-60	C	AJ238848
Poa pratensis				
(Kentucky blue	Poa p 1; group I	33	P	46
grass)	Poa p 5;	31/34	C	34,47
Sorghum halepense				
(Johnson grass)	Sor h 1;		C	48

C. Tree pollens

Fagales:

Alnus glutinosa				
(alder)	Aln g 1;	17	C	S50892
Betula verrucosa				
(birch)	Bet v 1;	17	C	see iso-list
	Bet v 2; profilin	15	C	M65179
	Bet v 3;		C	X79267
	Bet v 4;	8	C	X87153/S54819
	Bet v 6; isoflavone reductase homologue	33.5	C	AF135127
	Bet v 7; cyclophilin	18	P	P81531
Carpinus betulus				
(hornbeam)	Car b 1;	17	C	see iso-list
Castanea sativa				
(chestnut)	Cas s 1; Bet v 1 homologue	22	P	52
	Cas s 5; chitinase			
Corylus avellana				
(hazel)	Cor a 1;	17	C	see iso-list
Quercus alba				
(white oak)	Que a 1;	17	P	54

Lamiales:

Oleaceae:					
Fraxinus excelsior (ash)	Fra e 1;		20	P	58A
Ligustrum vulgare (privet)	Lig v 1;		20	P	58A
Olea europea (olive)	Ole e 1;		16	C	59,60
	Ole e 2;	profilin	15-18	C	60A
	Ole e 3;		9.2		60B
	Ole e 4;		32	P	P80741
	Ole e 5;	superoxide dismutase	16	P	P80740
	Ole e 6;		10	C	U86342
	Ole e 7;		?	P	P81430
Syringa vulgaris (lilac)	Syr v 1;		20	P	58A
Plantaginaceae:					
Plantago lanceolata (English plantain)	Pla l 1;		18	P	P842242
Pinales:					
Cryptomeria japonica (sugi)	Cry j 1;		41-45	C	55,56
	Cry j 2;			C	57, D29772
Cupressus arizonica (cypress)	Cup a 1;		43	C	A1243570
Juniperus ashei (mountain cedar)	Jun a 1;		43	P	P81294
	Jun a 3;		30	P	P81295
Juniperus oxycedrus (prickly juniper)	Jun o 2;	calmodulin-like	29	C	AF031471
Juniperus sabinoides (mountain cedar)	Jun s 1;		50	P	58
Juniperus virginiana (eastern red cedar)	Jun v 1;		43	P	P81825
D. Mites					
Acarus siro (mite)	Aca s 13;	fatty acid-bind.prot.	14*	C	AJ006774
Blomia tropicalis (mite)	Blo t 5;			C	U59102
	Blo t 12;	Bt11a		C	U27479
	Blo t 13;	Bt6 fatty acid-binding prot.		C	U58106

Dermatophagoides pteronyssinus				
(mite)	Der p 1; antigen P1	25	C	61
	Der p 2;	14	C	62
	Der p 3; trypsin	28/30	C	63
	Der p 4; amylase	60	P	64
	Der p 5;	14	C	65
	Der p 6; chymotrypsin	25	P	66
	Der p 7;	22-28	C	67
	Der p 8; glutathione transferase		C	67A
	Der p 9; collagenolytic serine prot.		P	67B
	Der p 10; tropomyosin	36	C	Y14906
	Der p 14; apolipophorin like p.		C	Epton p.c.
Dermatophagoides microceras				
(mite)	Der m 1;	25	P	68
Dermatophagoides farinae				
(mite)	Der f 1 ;	25	C	69
	Der f 2 ;	14	C	70,71
	Der f 3 ;	30	C	63
	Der f 10; tropomyosin		C	72
	Der f 11; paramyosin	98	C	72a
	Der f 14; Mag3, apolipophorin		C	D17686
Euroglyphus maynei				
(mite)	Eur m 14; apolipophorin	177	C	AF149827
Lepidoglyphus destructor				
(storage mite)	Lep d 2.0101;	15	C	73,74,75
	Lep d 2.0102;	15	C	75
E. Animals				
Bos domesticus				
(domestic cattle)	Bos d 2; Ag3,lipocalin	20	C	76,L42867
(see also foods)	Bos d 4; alpha-lactalbumin	14.2	C	M18780
	Bos d 5; beta-lactoglobulin	18.3	C	X14712
	Bos d 6; serum albumin	67	C	M73993
	Bos d 7; immunoglobulin	160		77
	Bos d 8; caseins	20-30		77
Canis familiaris				
(Canis domesticus)	Can f 1;	25	C	78,79
(dog)	Can f 2;	27	C	78,79
	Can f ?; albumin		C	S72946
Equus caballus				
(domestic horse)	Equ c 1; lipocalin	25	C	U70823
	Equ c 2; lipocalin	18.5	P	79A, 79B
Felis domesticus				
(cat saliva)	Fel d 1; cat-1	38	C	15
Mus musculus				
(mouse urine)	Mus m 1; MUP	19	C	80,81

Rattus norvegius				
(rat urine)	Rat n 1	17	C	82,83

F. Fungi

1. Ascomycota
1.1 Dothidiales

Alternaria alternata				
	Alt a 1;	28	C	U82633
	Alt a 2;	25	C	
	Alt a 3; heat shock prot. 70		C	U87807, U87808
	Alt a 4; prot.disulfidisomerase	57	C	X84217
	Alt a 6; acid.ribosomal prot P2	11	C	X78222, U87806
	Alt a 7; YCP4 protein	22	C	X78225
	Alt a 10; aldehyde dehydrogen.	53	C	X78227, P42041
	Alt a 11; enolase	45	C	U82437
	Alt a 12;acid.ribosomal prot P1	11	C	X84216
Cladosporium herbarum				
	Cla h 1;	13		83a, 83b
	Cla h 2;	23		83a, 83b
	Cla h 3; aldehyde dehydrogenase	53	C	X78228
	Cla h 4; acid.ribosomal prot P2	11	C	X78223
	Cla h 5; YCP4 protein	22	C	X78224
	Cla h 6; enolase	46	C	X78226
	Cla h 12;acid.ribosomal prot P1	11	C	X85180

1.2 Eurotiales

Aspergillus flavus				
	Asp fl 13; alkaline serine proteinase	34		84
Aspergillus fumigatus				
	Asp f 1;	18	C	M83781,S39330
	Asp f 2;	37	C	U56938
	Asp f 3; peroxisomal protein	19	C	U20722
	Asp f 4;	30	C	AJ001732
	Asp f 5; metalloprotease	42	C	Z30424
	Asp f 6; Mn superoxide dismutase	26.5	C	U53561
	Asp f 7;	12	C	AJ223315
	Asp f 8; ribosomal protein P2	11	C	AJ224333
	Asp f 9;	34	C	AJ223327
	Asp f 10; aspartic protease	34	C	X85092
	Asp f 11; peptidyl-prolyl isom	24		84a
	Asp f 12; heat shock prot. P90	90	C	85
	Asp f 13; alkaline serine proteinase	34		84b
	Asp f 15;	16	C	AJ002026
	Asp f 16;	43	C	g3643813
	Asp f 17;		C	AJ224865
	Asp f 18; vacuolar serine proteinase	34		84c

Aspergillus niger				
	Asp n 14; beta-xylosidase	105	C	AF108944
	Asp n 18; vacuolar serine proteinase	34	C	84b
	Asp n ?;	85	C	Z84377
Aspergillus oryzae				
	Asp o 13; alkaline serine proteinase	34	C	X17561
	Asp o 21; TAKA-amylase A	53	C	D00434,M33218
Penicillium brevicompactum				
	Pen b 13; alkaline serine Proteinase	33		86a
Penicillium citrinum				
	Pen c 3; peroxisomal membrane protein	18		86b
	Pen c 13; alkaline serine proteinase	33		86a
	Pen c 19; heat shock prot. P70	70	C	U64207
Penicillium notatum				
	Pen n 13; alkaline serine proteinase	34		89
	Pen n 18; vacuolar serine proteinase	32		89
	Pen n 20; N-acetyl glucosaminidase	68		87
Penicillium oxalicum				
	Pen o 18; vacuolar serine proteinase	34		89
1.3 Onygenales				
Trichophyton rubrum				
	Tri r 2;		C	90
	Tri r 4; serine protease		C	90
Trichophyton tonsurans				
	Tri t 1;	30	P	91
	Tri t 4; serine protease	83	C	90
1.4 Saccharomycetales				
Candida albicans				
	Cand a 1;	40	C	88
Candida boidinii				
	Cand b 2;	20	C	J04984, J04985
2 Basidiomycota				
2.1 Basidiolelastomycetes				
Malassezia furfur				
	Mala f 1;			91a

	Mala f 2; MF1 peroxisomal membrane protein	21	C	AB011804
	Mala f 3; MF2 peroxisomal membrane protein	20	C	AB011805
	Mala f 4;	35	C	Takesako,p.c.
	Mala f 5;	18*	C	AJ011955
	Mala f 6; cyclophilin homologue	17*	C	AJ011956
2.2 Basidiomycetes				
Psilocybe cubensis				
	Psi c 1;			
	Psi c 2; cyclophilin	16		91b
Coprinus comatus (shaggy cap)				
	Cop c 1; leucine zipper prot.	11	C	AJ132235
	Cop c 2;			Brander,p.c.
	Cop c 3;			Brander,p.c.
	Cop c 5;			Brander,p.c.
	Cop c 7;			Brander,p.c.
G. Insects				
Aedes aegyptii (mosquito)				
	Aed a 1; apyrase	68	C	L12389
	Aed a 2;	37	C	M33157
Apis mellifera (honey bee)				
	Api m 1; phospholipase A2	16	C	92
	Api m 2; hyaluronidase	44	C	93
	Api m 4; melittin	3	C	94
	Api m 6;	7-8	P	Kettner,p.c.
Bombus pennsylvanicus (bumble bee)				
	Bom p 1; phospholipase	16	P	95
	Bom p 4; protease		P	95
Blattella germanica (German cockroach)				
	Bla g 1; Bd90k		C	
	Bla g 2; aspartic protease	36	C	96
	Bla g 4; calycin	21	C	97
	Bla g 5; glutathione transf.	22	C	98
	Bla g 6; troponin C	27	C	98
Periplaneta americana (American cockroach)				
	Per a 1; Cr-PII		C	
	Per a 3; Cr-PI	72-78	C	98A
	Per a 7; tropomyosin	37	C	Y14854
Chironomus thummi thummi (midges)				
	Chi t 1-9; hemoglobin	16	C	99
	Chi t 1.01; component III	16	C	P02229
	Chi t 1.02; component IV	16	C	P02230
	Chi t 2.0101; component I	16	C	P02221
	Chi t 2.0102; component IA	16	C	P02221
	Chi t 3; component II-beta	16	C	P02222
	Chi t 4; component IIIA	16	C	P02231

	Chi t 5; component VI	16	C	P02224
	Chi t 6.01; component VIIA	16	C	P02226
	Chi t 6.02; component IX	16	C	P02223
	Chi t 7; component VIIB	16	C	P02225
	Chi t 8; component VIII	16	C	P02227
	Chi t 9; component X	16	C	P02228
Dolichovespula maculata				
(white face hornet)	Dol m 1; phospholipase A1	35	C	100
	Dol m 2; hyaluronidase	44	C	101
	Dol m 5; antigen 5	23	C	102,103
Dolichovespula arenaria				
(yellow hornet)	Dol a 5; antigen 5	23	C	104
Polistes annularies				
(wasp)	Pol a 1; phospholipase A1	35	P	105
	Pol a 2; hyaluronidase	44	P	105
	Pol a 5; antigen 5	23	C	104
Polistes dominulus				
(Mediterranean paper wasp)				
	Pol d 1;			DR Hoffman
	Pol d 4; serine protease	32-34	C	DR Hoffman
	Pol d 5;			P81656
Polistes exclamans				
(wasp)	Pol e 1; phospholipase A1	34	P	107
	Pol e 5; antigen 5	23	C	104
Polistes fuscatus				
(wasp)	Pol f 5; antigen 5	23	C	106
Polistes metricus				
(wasp)	Pol m 5; antigen 5	23	P	106
Vespa crabo				
(European hornet)	Vesp c 1; phospholipase	34	P	107
	Vesp c 5.0101; antigen 5	23	C	106
	Vesp c 5.0102; antigen 5	23	C	106
Vespa mandarina				
(giant asian hornet)	Vesp m 1.01;			DR Hoffman
	Vesp m 1.02;			DR Hoffman
	Vesp m 5;			P81657
Vespula flavopilosa				
(yellowjacket)	Ves f 5; antigen 5	23	C	106
Vespula germanica				
(yellowjacket)	Ves g 5; antigen 5	23	C	106
Vespula maculifrons				
(yellowjacket)	Ves m 1; phospholipase A1	33.5	C	108
	Ves m 2; hyaluronidase	44	P	109
	Ves m 5; antigen 5	23	C	104

Vespula pennsylvanica (yellowjacket)	Ves p 5;	antigen 5	23	C	106
Vespula squamosa (yellowjacket)	Ves s 5;	antigen 5	23	C	106
Vespula vidua (wasp)	Ves vi 5;		23	C	106
Vespula vulgaris (yellowjacket)	Ves v 1;	phopholipase A1	35	C	105A
	Ves v 2;	hyaluronidase	44	P	105A
	Ves v 5;	antigen 5	23	C	104
Myrmecia pilosula (Australian jumper ant)	Myr p 1;			C	X70256
	Myr p 2;			C	S81785
Solenopsis geminata (tropical fire ant)	Sol g 2;				DR Hoffman
	Sol g 4;				DR Hoffman
Solenopsis invicta (fire ant)	Sol i 2;		13	C	110,111
	Sol i 3;		24	C	110
	Sol i 4;		13	C	110
Solenopsis saevissima (brazilian fire ant)	Sol s 2;				DR Hoffman

H. Foods

Gadus callarias (cod)	Gad c 1;	allergen M	12	C	112,113
Salmo salar (Atlantic salmon)	Sal s 1;	parvalbumin	12	C	X97824 X97825
Bos domesticus (domestic cattle) (milk) (see also animals)	Bos d 4;	alpha-lactalbumin	14.2	C	M18780
	Bos d 5;	beta-lactoglobulin	18.3	C	X14712
	Bos d 6;	serum albumin	67	C	M73993
	Bos d 7;	immunoglobulin	160		77
	Bos d 8;	caseins	20-30		77
Gallus domesticus (chicken)	Gal d 1;	ovomucoid	28	C	114,115
	Gal d 2;	ovalbumin	44	C	114,115
	Gal d 3;	conalbumin (Ag22)	78	C	114,115
	Gal d 4;	lysozyme	14	C	114,115
	Gal d 5;	serum albumin	69	C	X60688
Metapenaeus ensis (shrimp)	Met e 1;	tropomyosin		C	U08008
Penaeus aztecus (shrimp)	Pen a 1;	tropomyosin	36	P	116

Penaeus indicus (shrimp)	Pen i 1; tropomyosin	34	C	117
Todarodes pacificus (squid)	Tod p 1; tropomyosin	38	P	117A
Haliotis Midae (abalone)	Hal m 1	49	-	117B
Apium graveolens (celery)	Api g 1; Bet v 1 homologue	16*	C	Z48967
	Api g 4; profilin			AF129423
	Api g 5;	55/58	P	P81943
Brassica juncea (oriental mustard)	Bra j 1; 2S albumin	14	C	118
Brassica rapa (turnip)	Bra r 2; prohevein-like protein	25	?	P81729
Hordeum vulgare (barley)	Hor v 15; BMAI-1	15	C	119
Zea mays (maize, corn)	Zea m 14; lipid transfer prot.	9	P	P19656
Oryza sativa (rice)	Ory s 1;		C	U31771
Corylus avellana (hazelnut)	Cor a 1.0401; Bet v 1 homologue	17	C	AF136945
Malus domestica (apple)	Mal d 1; Bet v 1 homologue		C	X83672
	Mal d 2; thaumatin homologue		C	AJ243427
	Mal d 3; lipid transfer protein	9	C	Pastorello
Pyrus communis (pear)	Pyr c 1; Bet v 1 homologue	18	C	AF05730
	Pyr c 4; profilin	14	C	AF129424
	Pyr c 5; isoflavone reductase homologue	33.5	C	AF071477
Persea americana (avocado)	Pers a 1; endochitinase	32	C	Z78202
Prunus armeniaca (apricot)	Pru ar 1; Bet v 1 homologue		C	U93165
	Pru ar 3; lipid transfer protein	9	P	
Prunus avium (sweet cherry)	Pru av 1; Bet v 1 homologue		C	U66076
	Pru av 2; thaumatin homologue		C	U32440
	Pru av 4; profilin	15	C	AF129425
Prunus persica (peach)	Pru p 3;lipid transfer protein	10	P	P81402

Sinapis alba (yellow mustard)	Sin a 1; 2S albumin	14	C	120
Glycine max (soybean)	Gly m 1.0101; HPS	7.5	P	121
	Gly m 1.0102; HPS	7	P	121
	Gly m 2	8	P	A57106
	Gly m 3; profilin	14	C	AJ223982
Arachis hypogaea (Peanut)	Ara h 1; vicilin	63.5	C	L34402
	Ara h 2; conglutin	17	C	L77197
	Ara h 3; glycinin	60	C	AF093541
	Ara h 4; glycinin	37	C	AF086821
	Ara h 5; profilin	15	C	AF059616
	Ara h 6; conglutin homolog	15	C	AF092846
	Ara h 7; conglutin homolog	15	C	AF091737
Actinidia chinensis (kiwi)	Act c 1; cysteine protease	30	P	P00785
Solanum tuberosum (potato)	Sola t 1; patatin	43	P	P15476
Bertholletia excelsa (Brazil nut)	Ber e 1; 2S albumin	9	C	P04403,M17146
Juglans regia (English walnut)	Jug r 1; 2S albumin		C	U66866
	Jug r 2; vicilin	44	C	AF066055
Ricinus communis (Castor bean)	Ric c 1; 2S albumin		C	P01089

I. Others

Anisakis simplex (nematode)	Ani s 1;	24	P	A59069
	Ani s 2; paramyosin	97	C	AF173004
Ascaris suum (worm)	Asc s 1;	10	P	122
Den n (red coral)	Den n 1;			Onizuka, p.c.
Hevea brasiliensis (rubber)	Hev b 1; elongation factor	58	P	123,124
	Hev b 2; (1,3-glucanase	34/36	C	125
	Hev b 3	24	P	126,127
	Hev b 4; component of microhelix protein complex	100/110/115	P	128
	Hev b 5	16	C	U42640
	Hev b 6.01 hevein precursor	20	C	M36986/p02877
	Hev b 6.02 hevein	5	C	M36986/p02877

	Hev b 6.03 C-terminal fragment	14	C	M36986/p02877
	Hev b 7; patatin homologue	46	C	U80598
	Hev b 8; profilin	14	C	Y15042
	Hev b 9; enolase	51	C	AJ132580/ AJ132581
	Hev b 10; Mn-superoxide dismut.	26	C	AJ249148
Ctenocephalides felis felis (cat flea)	Cte f 1;			
	Cte f 2; M1b	27	C	AF231352
Homo sapiens (human autoallergens)	Hom s 1;	73*	C	Y14314
	Hom s 2;	10.3*	C	X80909
	Hom s 3;	20.1*	C	X89985
	Hom s 4;	36*	C	Y17711
	Hom s 5;	42.6*	C	P02538

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